Inappropriate prescribing of preventative medication in patients with life limiting illness: a systematic review

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Abstract

Objectives: To systematically review the literature to examine the methods used to identify inappropriate prescribing of preventative medication in patients with life limiting illness and to detail the nature of medications prescribed.

Methods: A systematic literature search of four databases was undertaken (Medline, Embase, CINAHL, PsycINFO) from inception to April 2015 to identify peer-reviewed, observational studies assessing inappropriate prescribing of preventative medication in patients with life limiting illness. Inclusion criteria were: participants had a life limiting illness; prescribed/dispensed/using preventative medication; medication appropriateness assessed as a specific study aim or outcome.

Results: We found 19 studies meeting our eligibility criteria. The methods used to assess medication appropriateness included criteria developed for the elderly such as the Beers criteria, and STOPP criteria, Delphi consensus and expert clinical opinion. Lipid regulating drugs (12 studies), antihypertensive (11 studies) and anti-diabetic medications (9 studies) were the most common classes of inappropriate medication identified.

Conclusion: Patients with life limiting illnesses are prescribed preventative medications considered inappropriate in the context of diminished life expectancy. The way in which preventative medication appropriateness is assessed in patients with life limiting illness varies considerably – with some methodologies utilising criteria previously developed for elderly populations. Given this lack of standardisation, improving the prescribing in this context requires an approach that is specifically designed and validated for populations with life limiting illness.

Introduction

Polypharmacy and pill burden are common in patients with life limiting illness such as cancer, heart failure, renal disease and dementia.[1] A key priority for healthcare professionals, when caring for these patients, is balancing chronic disease management and palliation of acute symptoms. An important element of this process is ensuring that the benefit of any prescribing decisions outweighs the potential risks. This can be particularly challenging, as many co-morbidities are treated with chronic medications to maintain, or are prescribed to prevent further worsening of the disease state. Such preventative medications may not treat symptoms of the underlying disease; however, stopping preventative medications could, in theory, further worsen the co-morbidity, resulting in the exacerbation of symptoms.[2]

In the context of diminished life expectancy, prescribing preventative medications may be inappropriate given the time until benefit can be several years and patients are at increased risk of developing a drug-related toxicity due to their altering pharmacokinetic and pharmacodynamic profiles.[3, 4] To assist healthcare professionals in making prescribing decisions for this patient population, a series of frameworks have been developed to promote rational prescribing and reduce the use of unnecessary and potentially harmful care.[5, 6] However, despite these approaches, and the policy drivers advocating the use of preventative medication,[7] it is unclear to what extent preventative medications are prescribed for patients with life limiting illness. Therefore, this study aimed to systematically review the peer-reviewed literature to examine the methods used to identify inappropriate prescribing of preventative medication in patients with life limiting illness and to detail the nature of medications prescribed.

Methods

The review was carried out and reported according to the Preferred Reporting in Systematic Reviews and Meta-analyses (PRISMA) guidelines;[8] the protocol was registered with PROSPERO CRD42014013733.

Data sources

The following databases were searched to identify relevant studies: MEDLINE (Ovid), EMBASE (Ovid), CINAHL and PsycINFO. All databases were searched from their respective start dates to April 2015; studies were limited to those reported in English. The search strategy was modified, when appropriate, to suit syntax requirements (see Appendix 1); search terms were focused to title and abstract. The bibliographies of all included studies were hand searched; information was also requested from key experts in the field relating to on-goings studies.

Study selection

To be included in the review, studies had to meet the following criteria:

1. Population: patients with life limiting illness prescribed/dispensed/using preventative medication. For the purposes of the review, life limiting illness is defined as a malignant or non-malignant condition that would significantly reduce life expectancy including cancer, advanced dementia, advanced heart failure, end-stage chronic obstructive pulmonary disease (COPD) or advanced Parkinson's disease; preventative medication is defined as any medication used for primary, secondary or tertiary prevention to avert and avoid disease, including lipid regulating medication, anti-hypertensive medication, anti-diabetic medication, antiplatelet medication.
2. Study type: all types of observational studies including case series, cross sectional and cohort studies in routine care.
3. Outcomes: assessed medication 'appropriateness' (included specifically as a study aim or outcome measure) and whether preventative medication was discontinued in included studies.

Exclusion criteria

We excluded the following studies:

1. Those examining prescribing of preventative medication in populations without life limiting illness (e.g. elderly patients).

2. Those reporting prescribing/dispensing/medication use in patients with life limiting illnesses, without assessing medication appropriateness.
3. Those reported as a conference abstract.

Study selection and screening

The initial screening of titles and abstracts was conducted independently by two reviewers (IA and LL), with a random 10% of the sample checked by a third reviewer (AT). Full-paper study inclusion and data extraction was conducted independently by two reviewers (IA and LL); the following data was extracted from included studies: study objectives, population, setting, life limiting illness, methodology to assess medication appropriateness, primary outcome relating to inappropriate medication use, types of preventative medication (either class or individual medication), whether medication was discontinued as part of the study; comprehensiveness of reporting based on the STROBE checklist.[9] Any discrepancies were resolved through discussion and, if agreement was not reached, by consensus with the project lead (AT).

Data extraction quality appraisal

In the absence of a validated quality assessment tool suitable for all observational studies, including case series studies, we assessed the comprehensiveness of reporting using the STROBE checklist, based on ten key items from the guideline (items 2, 3, 5, 6-8, 10, 14, 16, 22).[9] This was done independently by two reviewers (IA and LL); any discrepancies were discussed and agreement was reached by consensus (AT).

Reporting

Due to the heterogeneity of study methodology and outcomes, we could not use traditional meta-analytic approaches to combine individual study results. Instead, we described key study features using a narrative approach across the included studies.

Results

Literature search

There were 20,343 hits generated from the initial literature search. After duplicates were removed, 13,472 studies were screened for eligibility, based on title and abstract; from this, 88 articles were selected for a full text review. After a full paper screen, 19 individual studies were included in the review; reasons for study exclusion were: not focused on preventative medications, not assessing medication appropriateness, not assessing patients with a life limiting illness, paper was a review of the literature, opinion piece/editorial, (Figure 1); included studies are summarised in Table 1.

Please insert Table 1 around here

Quality appraisal

All studies reported on the rationale, scientific background and settings of the work, as well as defining the sources of data. Two of the studies did not clearly state primary objectives,[11, 22] while only one provided justification of the sample size used.[17] The remaining studies recruited participants over a defined time period (either retro- or prospectively) or used pre-specified number of patients; neither approach stated a firm rationale or basis. Basic participant demographics, such as gender, age and details of life limiting illness, were reported in all but one of the studies.[24] Nine of the studies reported a funding source.[10, 12, 14, 20, 21, 25-28]

Participants

The total number of patients included in the studies was 10,220, ranging from 20 [26] to 5405 patients.[27] The most common life limiting illness described in the studies was cancer: nine studies examined medication use in different cancers,[11, 14, 15, 17, 19-23] while one study focused exclusively on patients with advanced lung cancer.[27] Four studies explored medication use in patients with dementia,[12,18, 25, 26] and two focused on patients with terminal illness in a palliative care environment;[24, 28] the most common condition in these studies was cancer, although patients with advanced heart failure, end stage COPD, and Parkinson's disease were also included. One study

explored how diabetes is managed in terminally ill patients;[16] the life limiting illness of each patient was not stated, and the study focused exclusively on anti-diabetic medication. The remaining studies included patients with advanced heart failure [10] and chronic kidney disease.[13]

Settings

Nine were based in hospitals,[10, 11, 13, 15, 16-18, 22, 27] three within palliative care settings,[14, 24, 28] three within outpatient oncology clinics,[19, 20, 23] one within a long-term care facility,[12] two within nursing homes,[25, 26] and one study compared medication use for patients attending a hospice and hospital.[21]

Criteria to assess medication appropriateness

The methodology used to assess medication appropriateness was wide ranging. Several studies used previously developed methodology to aid prescribing decisions in older people;[10, 13, 19, 20, 23, 24] these included the Screening Tool of Older Persons' potentially inappropriate Prescriptions (STOPP) criteria,[29] the Beers criteria [30] and the Unnecessary Drug Use Measure (which contains three items from the Medication Appropriateness Index [31]). In contrast to these approaches, Lindsay and colleagues, using the current literature as an evidence base, developed and validated their own guideline, the Onc-Pal deprescribing guideline, to assess medication appropriateness.[17]

Other studies utilised the opinion of the clinical experts to assess medication appropriateness: Fede and colleagues used this approach to develop a set of explicit criteria (e.g. using a statin when there was a lack of any cardiovascular event in the prior 12 months was considered inappropriate) to determine if a medication was considered 'futile',[11] while Rajimakers surveyed international experts to gather opinion on medication appropriateness and subsequently applied this to assess prescribing in a cohort of cancer patients.[21] Riechelmann also assessed medication futility but defined it as when there were no short-term benefit to patients with respect to survival, quality of life, or symptom control.[22] The methodologies developed by Fede and Riechelmann to assess

medication futility were also deployed by Kotlinska-Lemieszek [14] and Lee,[15] who assessed prescribing in cohorts of patients with terminal cancer.

Todd and colleagues assessed medication appropriateness by surveying the clinical team [27] or through a Dephi consensus of pharmacists and palliative care consultants;[28] both approaches used a conceptual framework to guide decision making that considered: remaining life expectancy; time until benefit; goals of care and treatment targets.[5] Similarly, Holmes and colleagues [12] also employed a Delphi process of 12 geriatricians to determine if the medication was: always appropriate, sometimes appropriate, rarely appropriate and never appropriate; the results from this study in terms of what constituents an inappropriate medication were applied to the work of Tjia [25, 26] who explored medication use in nursing residents with advanced dementia.

Types of inappropriate medication

The most common preventative class of medication assessed to be inappropriate were the lipid lowering agents – the most common of which were the statins; this was reported in the majority of studies.[11-15, 17, 18, 22, 25-28] Other classes of inappropriate medication identified included vitamins and mineral supplements,[11, 14, 18, 20, 22, 24, 28] antidiabetic,[10, 11, 13, 15-19, 24] antihypertensive,[10, 11, 13-15, 17-19, 21, 23, 28] antiplatelet [10, 12, 17-19, 26-28] and antiulcer medication.[14, 17, 19, 21, 27]

Discussion

The review identified a number of studies demonstrating that preventative medications are prescribed inappropriately to patients with various life limiting illnesses. The class of medication most commonly identified as inappropriate or 'futile' were the lipid lowering agents – with statins being the most frequent. This finding is supported by several cohort studies that show statins continue to be prescribed in patients with diminished life expectancy,[32, 33] while it is also acknowledged that being diagnosed with a life limiting illness does not decrease statin use in that patient subgroup.[34] The use of statins in life limiting illness has also been acknowledged by the Choosing Wisely

initiative who recommend to avoid the routine use of lipid-lowering medications in patients with limited life expectancy.[35] Our review demonstrates that lipid-lowering medications are being prescribed to patients within this context, but it is too early to ascertain if this policy recommendation has changed prescribing behaviour in practice. This observation is also timely considering the policy shift across the world to lower the threshold criteria to initiate statin therapy, which will significantly increase the number of patients taking a statin for primary prevention.[36, 37]

Our review demonstrated a range of methodologies assessing medication appropriateness; several studies used expert opinion or based the decisions on the literature, while others utilised methodology originally developed to aid prescribing decisions in older people. Lipid-lowering agents were the class of preventative medications most commonly identified as inappropriate in our review yet studies that used the STOPP criteria, Beers criteria or Unnecessary Drug Use Measure did not assess lipid-lowering medication as inappropriate, as this class of drugs are not part of these instruments. Indeed, as many of these instruments were originally designed to assess medication appropriateness in an elderly population, the utility in patients' with life limiting illness may be inadequate and, in some cases, counter intuitive. Given this lack of standardisation, improving the prescribing in this context requires an approach that is specifically designed and validated for populations with life limiting illness. More support – possibly in the form of clear practical guidelines – should be made available to all healthcare professionals with responsibility for prescribing medication to patients with life limiting illness.

In recent years, the term 'deprescribing' – a way of rationalising medication that provides a limited benefit to patients – has been introduced to the world of pharmaceutical care. A timely article by Scott and colleagues, presenting a simple 5-step protocol to support deprescribing, define it as the systematic process of identifying and discontinuing drugs in instances in which existing or potential harms outweigh existing or potential benefits within the context of an individuals patient's care goals, current level of functioning, life expectancy, values and preferences.[38]. Indeed, our work in the context of life limiting illness, supports the concept of deprescribing and demonstrates that it should

be incorporated into all aspects of the prescribing process; many guidelines only state when to start a medication, but seldom explained when and how to discontinue or deprescribe a medication. From the studies identified in our review, only one, by Brunet and colleagues [18], actively discontinued or deprescribed inappropriate preventative medication. For this study, over 60 per cent of preventative medication was stopped due to a lack of an evidence base, with the majority of medication indicated for primary prevention. Unfortunately, this study did not ascertain how stopping preventative medication affected patients long-term.

There is a dearth of literature exploring how deprescribing preventative medication amongst patients with life limiting illness affects patient outcomes. Garfinkel has shown that stopping medication in a frail elderly population can be associated with improved quality of living and reduced mortality rates.[39] At present, it is not clear if these benefits are directly transferable to stopping medication in patients with life limiting illnesses. Of note, a recent randomised trial on statin discontinuation in patients with anticipated life expectancy from one month to one year, showed the rate of death was similar between the two groups, while the group that discontinued the statins had a longer median time-to-death (229 days compared to 190 days).[40] The trial also showed that the patients who discontinued the statins had a better quality of life, compared to those that continued statin therapy. This is significant progress, but given our work shows that antihypertensive and anti-diabetic medications are also frequently – and perhaps inappropriately – prescribed to patients with life limiting illness, it would be prudent to focus future trials on these medications to establish evidence-based approaches to deprescribing medication.

Another aspect of deprescribing also warranting further exploration is how patients perceive medication discontinuation when they have a life limiting illness. This is clearly a complex area, but it is conceivable that when a patient is diagnosed with a life limiting illness, they may view the value and benefit of preventative medication differently, in a light of a change in life expectancy. This may also be true for healthcare professionals who are involved in the prescribing decisions of those patients. A study investigating decision-making associated with prescribing in elderly patients

showed that GPs perceive discontinuing preventative medication as more challenging when compared to discontinuing medication indicated to treat acute conditions.[41] While Sand *et al*, who explored medication use in a group of patients with advanced cancer, showed there was a desire to reduce the number of tablets they take, as the medication reminded them of their illness.[42] A qualitative study building on these findings exploring preventative medication discontinuation in life limiting illness from the viewpoint of prescribers and patients would therefore be valuable.

There have been several reviews undertaken to identify inappropriate prescribing in patients with diminished life expectancy, although none have systematically reviewed the literature to examine the methods used to identify inappropriate prescribing of preventative medication in patients with life limiting illness. The most recent, a review by Lindsay *et al* [43], focused exclusively on cancer patients and concluded that there is evidence that potentially inappropriate medications (PIMs) are commonly prescribed in cancer patients. A recent review by Tjia and colleagues [44], who focussed on intervention studies that reduced unnecessary medication in frail elderly patients, concluded that there has was a lack of robust high quality evidence in this area and more work was needed to inform evidence based approaches to deprescribing medication. Our work, which is the first to systematically review the literature in relation to inappropriate preventative medication use in life limiting illness, builds on these findings and shows many patients in this context – not just those with cancer, as identified by Lindsay *et al* – continue to take preventative medication inappropriately.

While we believe our results are robust and have important implications for prescribing preventative medication to patients with life limiting illness, we acknowledge that our work has limitations. Firstly, the definition we used for preventative medication is broad. It is possible that some medications we considered preventative included in the review also have an affect on the control of acute symptoms (*e.g.* treating hyperglycaemia with an antidiabetic medication may relieve symptoms associated with fatigue as well as preventing long term complications), which may be beneficial to the patient. Secondly, as with all reviews, this systematic review may be subject to publication bias: it is possible that observational studies that did not show inappropriate prescribing in patients with life

limiting illness have a lower chance of being published, meaning that we have over-estimated the extent of inappropriate prescribing. We acknowledge these factors as limitations of our work; the results of this review should be interpreted with this in mind.

Conclusion

Patients with life limiting illnesses are commonly prescribed preventative medications that are considered inappropriate in the context of diminished life expectancy. The way in which preventative medication appropriateness is assessed in patients with life limiting illness varies considerably – with some methodologies utilising criteria that were previously developed for elderly populations. Given the lack of standardisation, improving the prescribing for patients with life limiting illness requires a new approach. Consideration should therefore be given to incorporating deprescribing approaches into clear practical treatment guidelines.

Funding/disclaimers

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. Conflicts of interest: none.

Ethics approval

Ethical approval was not required for this systematic review given the research did not involve participants or the use of their data.

Author	Objective	Setting	Population	Methods used to assess appropriateness	Study Outcome	Examples of preventative medication considered inappropriate	Discontinued as part of the study	Quality score
Barcelo (2014) Spain [10]	Analysed the appropriateness of medication prescribed to patients with heart failure with an estimated median survival time of less than 6 months	Geriatric ward	Advanced heart failure n=72	STOPP criteria	20 medications considered inappropriate	Calcium channel blockers, clopidogrel, alpha blockers, aspirin, chlorpropamide,	No	7
Fede (2011) Brazil [11]	Identified medications that were considered unnecessary as defined by explicit criteria that considered whether drugs could benefit patients with terminal cancer	Hospital	Advanced cancer n=87	Explicit criteria developed by the literature and expert opinion (2 oncologists and palliative care physician)	21 patients using inappropriate medication	Metformin, calcium supplements, captopril, vitamin B, statins	No	6
Holmes (2008) USA [12]	Evaluated the feasibility of developing consensus recommendations for appropriate prescribing for patients with advanced dementia. From this, the frequency of inappropriate prescribing was determined in a cohort of patients with advanced dementia	Long-term care facilities	Advanced dementia n=34	Expert consensus panel through Delphi technique (12 geriatricians)	10 patients using inappropriate medication	Clopidogrel, statins	No	7
Jones (2013) UK [13]	Examined the prevalence of potentially inappropriate medication in elderly patients with chronic kidney disease	Hospital	Chronic kidney disease (stages 3-5; average eGFR 17.2 mL/min) n=100	Beers criteria and BNF guidance for prescribing in patients with renal impairment	56 patients were prescribed one or more potentially inappropriate medication	Antihypertensive agents, antidiabetic agents, lipid lowering agents	No	6
Kotlinska-Lemieszek	Analysed medication use and identified unneeded drugs among a	Palliative care and	Cancer	When the medications are	Approximately 45% of patients used at	Lipid-lowering drugs, vitamins, minerals,	No	6

(2014) Europe [14]	cohort of patients with advanced cancer and pain who were using Step III opioids	cancer centres	n=2282	not thought to have beneficial effect on symptom control, quality of life or survival (from [11, 22])	least one drug categorised as unnecessary or potentially unnecessary	cardiovascular agents, gastroprotective agents		
Lee (2013) Korea [15]	Evaluated the prescribing of medication as essential or futile in terminal cancer patients	Haemato-oncology department within a hospital setting	Terminal cancer (progressed advanced cancer with life expectancy of less than 6 months) n=196	When the medications are not thought to have beneficial effect on symptom control, quality of life or survival (from [11, 22])	87 medications considered inappropriate	Anti-hypertensives, anti-diabetics, statins	No	6
Lim (2009) UK [16]	Established how diabetes is monitored and managed in terminally-ill diabetic patients	Hospital	Terminally ill patients with type 2 diabetes n=25	Standards based on the literature	2 patients using inappropriate medication	Oral hypoglycaemic medication and insulin	No	7
Lindsay (2014) Australia [17]	Designed and validated a deprescribing guideline for palliative cancer patients; a descriptive analysis was undertaken to identify potentially inappropriate medication	Hospital	Cancer (progressed advanced cancer with life expectancy of less than 6 months) n=61	OncPal describing Guideline developed by the authors (compared to an expert panel as a way of validation)	43 patients using inappropriate medication	Aspirin, anticoagulants, anti-hypertensives, dyslipidaemic agents, oral hypoglycaemics, agents used for peptic ulcer prophylaxis	No	8
Molist Brunet (2013) Spain [18]	Described the re-orientation of drug therapy using a patient centred approach with a multidisciplinary team to review medication; review	Acute geriatric unit	Advanced Dementia n=73	Multidisciplinary team (2 geriatricians and pharmacist)	Number of inappropriate medications not stated	Antiplatlets, antihypertensives, hypolypidemics, anticoagulants,	Yes	6

	established new therapeutic objectives based on end-of-life care			with the patient/carer (3 point patient centred medication therapy plan)		antidiabetics, nutritional supplements		
Nightingale (2015) USA [19]	Retrospectively examined medication use in ambulatory senior adults with cancer to determine prevalence of polypharmacy and potentially inappropriate medication use	Outpatient oncology clinic	Cancer n=234	Beers criteria STOPP HEDIS	94 patients using a potentially inappropriate medication (Beers) 88 patients using a potentially inappropriate medication (STOPP) 49 patients using a potentially inappropriate medication (HEDIS criteria)	Antiplatelet, long-acting sulfonylureas, sliding scale insulin, hydrochlorothiazide	No	6
Prithviraj (2012) USA [20]	Identified patient characteristics associated with polypharmacy and inappropriate medication use among older patients with a recent cancer diagnosis	Oncology clinic	Cancer n=117	Beers criteria	The prevalence of potentially inappropriate medication use was 44%	Iron supplements, digoxin	No	9
Raijmakers (2013) Italy [21]	Described medication use and assessed for potentially in terminally ill cancer patients and	Hospital and hospice	Cancer n=195	List generated through a survey with international experts	327 medications considered inappropriate	Anticoagulants, antihypertensives, antiulcer drugs	No	7
Riechelman n (2009) Canada [22]	Assessed futile (when no short-term benefit with respect to survival, quality of life, or symptom control was anticipated) medication use in	Palliative care clinic within a hospital	Advanced cancer n=372	Medication profile was reviewed by researchers	82 patients using inappropriate medication	Statins, multivitamins, allopurinol, folic acid, ferrous gluconate, fenofibrate	No	5

	terminally ill cancer patients	setting						
Saarelainen (2014) Australia [23]	Investigated the prevalence and factors associated with the use of potentially inappropriate medication in patients presenting to an oncology clinic	Oncology outpatient clinic	Cancer n=385	Beers criteria	102 patients using at least one potentially inappropriate medication	Prazosin	No	8
Suhri (2009) USA [24]	Evaluated if a geriatric palliative care team reduced unnecessary medication prescribing for elderly veterans with a life limiting illness	Geriatric palliative care unit	Terminal illness (dementia, cancer, heart failure) n=89	Unnecessary Drug Use Measure, which contains 3 items from the Medication Appropriateness Index	104 medications considered inappropriate	Vitamins, antithrombotic agents, endocrine agents	No	6
Tjia (2010) USA [25]	Examined medication use in patients with advanced dementia; study also assessed medications that were "never appropriate" in advanced dementia	Nursing homes	Advanced dementia n=323	Uses classification system from Holmes *et al* [12]	121 patients using inappropriate medication	Lipid lowering agents	No	9
Tjia (2014) USA [26]	Estimated the prevalence of medications with questionable benefit in nursing home residents with advanced dementia	Nursing homes	Advanced dementia n=5406	Uses criteria from Holmes *et al* [12]	2911 patients received at least one medication with questionable benefit	Lipid lowering agents, antiplatelet agents (excluding aspirin)	No	9
Todd (2013) UK [27]	Assessed the prevalence of inappropriate medication in lung cancer patients taking erlotinib	Hospital	Advanced lung cancer n=20	Clinical team (oncologist, pharmacist and nurse) using Holmes *et al* framework [5]	19 patients using inappropriate medication	Proton pump inhibitors, aspirin, clopidogrel, statins	No	6
Todd (2014) UK [28]	Assessed the prevalence of inappropriate medication use in a hospice population; potential drug-drug interactions were also identified and it was ascertained how many could be prevented by discontinuing	Tertiary palliative care centre	Terminal illness (cancer, end-stage COPD, heart	Modified Delphi consensus using Holmes *et al* framework [5]	92 patients using inappropriate medication	Statins, vitamin and mineral supplements, aspirin (for antiplatelet therapy), clopidogrel, ACE inhibitors, fenofibrate, calcium channel blockers, ezetimbe,	No	8

	inappropriate medication.		failure, Parkinson's disease) n=132			angiotensin II receptor antagonists		

Appendix 1: An example search strategy used for the Medline (Ovid) platform.

1. Inappropriate med*

2. Discontinu* med*

3. Unnecessary med*

4. Inappropriate prescribing

5. Deprescrib*

6. Med* optimi$ation

7. Med* rationali$ation

8. Med* futil*

9. Non-essential med*

10. Polypharmacy

11. Statin

12. Antihypertens*

13. Bisphosphonate

14. Vitamins

15. Minerals

16. Antiplatelet

17. Combine 1-16

18. Limited life expectancy

19. Diminished life expectancy

20. Poor prognosis

21. Palliative

22. Life limiting illness

23. End of life

24. Terminal*

25. Advanced

26. Oncology

27. Cancer

28. Chronic kidney disease

29. End stage renal failure

30. Chronic COPD

31. End stage COPD

32. Advanced dementia

33. Advanced heart failure

34. Combine 18-33

35. Combine 17 and 34.

References

1. Koh NY, Koo WH. Polypharmacy in palliative care: can it be reduced? *Singapore Med J.* 2002;43(6):279-83.

2. Iyer S, Naganathan V, McLachlan AJ, *et al*. Medication withdrawal trials in people aged 65 years and older. *Drugs Aging* 2008;25:1021-31.

3. Lee SJ, Leipzig RM, Walter LC. Incorporating lag time to benefit into prevention decisions for older adults. *JAMA.* 2013;310(24):2609-10.

4. Riechelmann RP, Zimmermann C, Chin SN, *et al*. Potential drug interactions in cancer patients receiving supportive care exclusively. *J Pain Symptom Manage.* 2008;35:535-43.

5. Holmes HM, Hayley DC, Alexander GC, *et al*. Reconsidering medication appropriateness for patients late in life. *Arch Intern Med*. 2006;166(6):605-9.

6. Stevenson J, Abernethy AP, Miller C, *et al*. Managing comorbidities in patients at the end of life. *BMJ*. 2004;329(7471):909-12.

7. Wider use of statins could cut deaths from heart disease. National Institute of Health and Care Excellence. Available at: https://www.nice.org.uk/news/article/wider-use-of-statins-could-cut-deaths-from-heart-disease (accessed 22.05.2015)

8. Liberati A, Altman DG, Tetzlaff J, *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ.* 2009;339:b2700.

9. STROBE statement. Strengthening reporting in observational studies. Available at: http://strobe-statement.org/index.php?id=available-checklists (accessed 22.05.2015)

10. Barceló M, Torres O, Ruiz D, *et al*. Appropriateness of medications prescribed to elderly patients with advanced heart failure and limited life expectancy who died during hospitalization. *Drugs Aging.* 2014;31(7):541-6.

11. Fede A, Miranda M, Antonangelo D, *et al*. Use of unnecessary medications by patients with advanced cancer: cross-sectional survey. *Support Care Cancer*. 2011;19:1313-18.

12. Holmes HM, Sachs GA, Shega JW, *et al*. Integrating palliative medicine into the care of persons with advanced dementia: identifying appropriate medication use. *J Am Geriatr Soc.* 2008;56(7):1306-11.

13. Jones SA, Bhandari S. The prevalence of potentially inappropriate medication prescribing in elderly patients with chronic kidney disease. *Postgrad Med J.* 2013;89(1051):247-250.

14. Kotlinska-Lemieszek A, Paulsen O, Kaasa S, *et al*. Polypharmacy in patients with advanced cancer and pain: A european cross-sectional study of 2282 patients. *J Pain Symptom Manage.* 2014;48(6):1145-1159.

15. Ran Lee HR, Yi SY, Kim DY. Evaluation of prescribing medications for terminal cancer patients near death: essential or futile. *Cancer Res Treat.* 2013;45(3):220–5.

16. Lim MY. Audit on the management of diabetes in terminally-ill medical patients. *Prog Palliative Care*. 2009;17(6):302-6.

17. Lindsay J, Dooley M, Martin J, *et al*. The development and evaluation of an oncological palliative care deprescribing guideline: the 'OncPal deprescribing guideline'. *Support Care Cancer.* 2015;23(1):71-8.

18. Molist Brunet N, Sevilla-Sanchez D, Amblas Novellas J, *et al*. Optimizing drug therapy in patients with advanced dementia: A patient-centered approach. *Eur Geriatric Medicine*. 2014;5(1):66-71.

19. Nightingale G, Hajjar E, Swartz K, *et al*. Evaluation of a pharmacist-led medication assessment used to identify prevalence of and associations with polypharmacy and potentially inappropriate medication use among ambulatory senior adults with cancer. *J Clin Oncol.* 2015;33(13):1453-9.

20. Prithviraj GK, Koroukian S, Margevicius S, *et al*. Patient characteristics associated with polypharmacy and inappropriate prescribing of medications among older adults with cancer. *J Geriatr Oncol.* 2012;3(3):228-237.

21. Raijmakers NJ, van Zuylen L, Furst CJ, *et al*. Variation in medication use in cancer patients at the end of life: a cross-sectional analysis. *Support Care Cancer*. 2013;21(4):1003-11.

22. Riechelmann RP, Krzyzanowska MK, Zimmermann C. Futile medication use in terminally ill cancer patients. *Supportive Care Cancer*. 2009;17(6):745-8.

23. Saarelainen LK, Turner JP, Shakib S, *et al*. Potentially inappropriate medication use in older people with cancer: prevalence and correlates. *J Geriatr Oncol.* 2014;5(4):439-46.

24. Suhrie EM, Hanlon JT, Jaffe EJ, *et al*. Impact of a geriatric nursing home palliative care service on unnecessary medication prescribing. *Am J Geriatr Pharmacother.* 2009;7(1):20-5.

25. Tjia J, Rothman MR, Kiely DK, *et al*. Daily medication use in nursing home residents with advanced dementia. *J Am Geriatr Soc.* 2010;58(5):880-8.

26. Tjia J, Briesacher BA, Peterson D, *et al*. Use of medications of questionable benefit in advanced dementia. *JAMA Intern Med.* 2014;174(11):1763-71.

27. Todd A, Williamson S, Husband A, *et al*. Patients with advanced lung cancer: is there scope to discontinue inappropriate medication? *Int J Clin Pharm.* 2013;35:181-4.

28. Todd A, Nazar H, Pearson S, *et al*. Inappropriate prescribing in patients accessing specialist palliative day care services. *Int J Clin Pharm.* 2014;36(3):535-43.

29. Gallagher P, Ryan C and Byrne S. STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. *Int J Clin Pharmacol Ther*. 2008;46:72-83.

30. Fick DM, Cooper JW, Wade WE, *et al*. Updating the Beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts. *Arch Intern Med.* 2003;163:2716-24.

31. Hanlon JT, Schmader KE, Samsa GP, *et al*. A method for assessing drug therapy appropriateness. *J Clin Epidemiol.* 1992;45:1045–51.

32. Stavrou EP, Buckley N, Olivier J, *et al*. Discontinuation of statin therapy in older people: does a cancer diagnosis make a difference? An observational cohort study using data linkage. *BMJ Open.* 2012;2:e000880.

33. Tjia J, Cutrona SL, Peterson D, *et al*. Statin discontinuation in nursing home residents with advanced dementia. *J Am Geriatr Soc.* 2014;62(11):2095-101.

34. Silveira MJ, Kazanis AS, Shevrin MP. Statins in the last six months of life: a recognizable, life-limiting condition does not decrease their use. *J Palliat Med.* 2008;11(5):685-93.

35. AMDA – The Society for Post-Acute and Long-Term Care Medicine: Five Things Physicians and Patients Should Question. Available at: http://www.choosingwisely.org/doctor-patient-lists/amda/ (accessed 22.02.2015)

36. Pencina MJ, Navar-Boggan AM, D'Agostino RB, Sr., *et al*. Application of new cholesterol guidelines to a population-based sample. *N Engl J Med.* 2014;370(15):1422-31.

37. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. NICE Clinical Guideline 181. NICE Clinical Guideline 181. Available at: http://www.nice.org.uk/guidance/cg181/resources/guidance-

lipid-modification-cardiovascular-risk-assessment-and-the-modification-of-blood-lipids-for-the-primary-and-secondary-prevention-of-cardiovascular-disease-pdf (accessed 22.05.2015)

38. Scott IA, Hilmer SN, Reeve E, *et al*. Reducing inappropriate polypharmacy: the process of deprescribing. *JAMA Intern Med.* 2015 Mar 23. doi: 10.1001/jamainternmed.2015.0324.

39. Garfinkel D, Zur-Gil S, Ben-Israel J. The war against polypharmacy: a new cost-effective geriatric-palliative approach for improving drug therapy in disabled elderly people. *Isr Med Assoc J.* 2007;**9**(6):430-4.

40. Kutner JS, Blatchford PJ, Taylor DH, *et al*. Safety and benefit of discontinuing statin therapy in the setting of advanced, life-limiting illness: a randomized clinical trial. *JAMA Intern Med.* 2015; doi: 10.1001/jamainternmed.2015.0289.

41. Schuling J, Gebben H, Veehof LJ, *et al*. Deprescribing medication in very elderly patients with multimorbidity: the view of Dutch GPs. A qualitative study. *BMC Fam Pract.* 2012;13:56.

42. Sand AM, Harris J, Rosland JH. Living with advanced cancer and short life expectancy: patients' experiences with managing medication. *J Palliat Care.* 2009; 25(2):85-91.

43. Lindsay J, Dooley M, Martin J, Fay M, Kearney A, Barras M. Reducing potentially inappropriate medications in palliative cancer patients: evidence to support deprescribing approaches. *Support Care Cancer*. 2014;22(4):1113-9.

44. Tjia J, Velten SJ, Parsons C, *et al*. Studies to reduce unnecessary medication use in frail older adults: a systematic review. *Drugs Aging.* 2013;30(5):285-307.